United States Patent [19]

Pearlman

[11] **Patent Number: 4,853,388**

[45] **Date of Patent: Aug. 1, 1989**

[54] **METHOD FOR TREATING PSORIASIS WITH CYTOTOXIC AGENTS**

[76] Inventor: **Dale L. Pearlman**, 21063 Christensen Dr., Cupertino, Calif. 95014

[21] Appl. No.: **50,983**

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[51] **Int. Cl.**[4] **A61K 31/505**

[52] **U.S. Cl.** **514/274**; 514/863

[58] **Field of Search** 514/274, 563

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,989,816	11/1976	Rajadhyaksha	424/60
4,423,040	12/1983	Rajadhyaksha	424/180
4,636,509	1/1987	Phillipps et al.	514/274
4,705,791	11/1987	Bemeche et al.	514/274

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Pearlman et al., J. Am. Acad. Dormatol. vol. 17, No. 1, pp 78–82 (1987).

Pearlman et al. J. Am. Acad. Dermotol. 15:1247–52, 1986.

Peck et al., "Topical Lomustine in the Treatment of Psoriasis." Arch. Derm. 106:172–176 (1972).

Primary Examiner—Leonard Schenkman

Attorney, Agent, or Firm—William B. Walker

[57] **ABSTRACT**

A method for treating psoriasis comprising applying an effective amount of a cytotoxic drug dispersed in a pharmaceutically acceptable vehicle containing a penetrating solvent for the drug, the drug being applied to the skin area affected by the psoriasis without occlusion in pulses of from 1 to 3 applications per pulse, the pulses being applied at an interval of once every from 3 to 30 days and preferably at an interval of from 4 to 14 days. Optimally, the penetrating solvent is free from toxic effects, such as AZONE or similar substituted azacycloalkyl-2-ones, tertiary amine oxides, and the like.

10 Claims, No Drawings

METHOD FOR TREATING PSORIASIS WITH CYTOTOXIC AGENTS

FIELD OF THE INVENTION

This invention relates to the therapeutic treatment of skin disorders such as psoriasis. In particular, this invention relates to an effective regimen for successfully treating psoriasis with a cytotoxic agent such as 5-fluorouracil in a penetrating solvent.

BACKGROUND OF THE INVENTION

Psoriasis is a chronic, hereditary, recurrent, papulosquamous dermatosis, the distinctive lesion of which is a vivid red macule, papule, or plaque covered almost to its edge by silvery lamellated scales. It usually involves the scalp and extensor surfaces of the limbs, especially the elbows, knees and shins.

Traditional treatments of psoriasis have included daily or more frequent application of corticosteroids such as betamethasone acetate, betamethasone valerate, fluocinolone acetonide, fluocinolone acetonide acetate, and the like dissolved or suspended in an ointment, lotion, or glycol solvent to the affected area. Occlusive techniques such as wrapping cortiocoid treated areas with a moisture-impermeable wrapping such as a self-attracting plastic film such as polyvinylidene chloride film (SARAN) has been found to increase the effectiveness of the treatment. Penetrating solvents have been investigated for enhancing percutaneous absorption of these drugs in an effort to more successfully treat more resistive conditions.

DESCRIPTION OF THE PRIOR ART

Fluorouracil (5-fluorouracil or 5-FU) is described as useful for the treatment of actinic keratosis, applied topically as a 1% cream or solution, once or twice daily, to the affected area in REMINGTON'S PHARMACEUTICAL SCIENCES. Mack Publishing: Easton, 15th ed. p 1079 (1975).

AZONE (1-dodecylazacycloheptan-2-one) is reported to enhance the percutaneous absorption of a variety of drugs including steroids and fluorouracil by Stoughton, R., *Arch.Dermatol.* 118:474–477 (1982). Prior use of dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), dimethyl formamide (DMF), 1-methyl-2-pyrrolidone, and propylene glycol to enhance skin penetration of drugs was also disclosed.

Comparison of AZONE with other penetrating solvents such as propylene glycol and n-decylmethyl sulfoxide for enhancing penetration of fluorouracil is described by Touitou, E., *International Journal of Pharmaceutics.* 27:89–98 (1985). The writer characterizes 5-FU as a cytotoxic agent used topically on the skin in actinic kerotosis and various epithelial neoplasma, and states the need for improved therapy brought into use methods for increasing skin penetration such as use of occlusivity and chemical enhancing agents, citing Chen, Y., NOVEL DRUG DELIVERY SYSTEMS. Marcel Dekker: New York, p 192 (1982). Propylene glycol solutions are said to be the most popular, and the writer's presentation demonstrated that AZONE was a more effective penetrating agent than propylene glycol or n-decylmethyl sulfoxide in dilute concentrations. Sogibayashi, K. et al, *J. Pharm.Pharmacol.* 37:578–580 (1985) and Mourmoto, Y. et al, *International Journal of Pharmacology.* 32:31–38(1986) also describe enhanced absorption with AZONE across hairless rat skin, using 5-fluorouracil as a model drug.

U.S. Pat. No. 3,989,816 describes n-alkylazacycloheptan-2-ones wherein the alkyl group has from 1 to 18 carbons, and the use of these and related compounds to enhance percutaneous absorption or penetration of drugs. Among the extensive lists of drugs are antineoplastic agents such as fluorouracil. Treatment of psoriasis with steroids in the penetrating solvent is also disclosed. U.S. Pat. Nos. 3,989,815 and 3,991,203 describe use of bis-azacyclopentan-only alkanes and 1-substituted azacyclopentan-2-ones, respectively, as penetrating agent. In a disclosure almost identical to U.S. Pat. No. 3,989,816, the inventor describes the treatment of psoriasis with steroids in the respective solvents, and lists fluorouracil as a suitable antineoplastic agent for use with the solvents.

U.S. Pat. No. 2,802,005 claims fluorouracil and describes it use as a germicidal agent or antimetabolite.

U.S. Pat. No. 4,565,806 describes treatment of skin cancer with cytostatic agents such as fluorouracil, colchicine, vinblastin sulfate, phloridzin, triethylene thiophosphamide, humic acid, and nitrogen mustards such as cyclophosphamide and mechlorethamine in DMSO. Percutaneous or intravenous administration are described. Suitable dosage levels and frequency recommended are said to be known to those skilled in the art.

U.S. Pat. No. 4,411,893 describes a novel water-soluble tertiary amine oxide useful to enhance of penetration of drugs through the skin. U.S. Pat. No. 3,326,768 is cited in the patent to show the use of a phosphine oxide surfactant in a topical preparation. U.S. Pat. No. 3,472,931 is also referenced, disclosing the use of a vehicle containing a lower alkyl amide to enhance percutaneous absorption. Use of the absorption enhancers with hydrocortisone to treat inflammation and with 5-fluorouracil for the treatment of actinic keratosis is also disclosed.

U.S. Pat. No. 3,996,924 describes the treatment of psoriasis with a combination of corticosteroid and 5-fluorouracil in a suitable topical ointment or solution carrier. Included in an omnibus listing of possible carrier ingredients are propylene glycols, dimethyl sulfoxide and dimethyl formamide. Daily application, preferably with a continuous occlusive dressing is recommended.

The prior art describes the application of cytotoxic agents in penetrating solvents applied once or more daily. Concurrent use with an occlusive dressing is indicated. In fact, the extreme inflammatory reaction caused by the cytotoxic damage to treated skin seen in continuous daily dosing schedules has heretofore prevented the practical use of these solvent systems to enhance percutaneous absorption of cytotoxic agents.

The use of 5% fluorouracil solutions topically with traditional vehicles under continuous occlusion for 2 weeks have been reported by Tsuiji, T. et al. *Arch.Dermatol.* 105:208–212 (1972) as effective therapy for psoriasis, producing long remissions without systemic toxicity. However, the therapy produced such severe burns that hospitalization of the patient was required. When fluorouracil was applied every other day (3 times a week) with occlusion, erosions also occurred, limiting therapy, and remission was brief. Ljunggren, B. et al, *Arch.Dermatol.* 106:263 (1972). When fluorouracil was used without occlusion, and with a topical steroid continuously for 2 weeks, the degree of local toxicity was acceptable, but the degree of improvement and the

duration of remission was not sufficient. Fredriksson, T., "Topical treatment of psoriasis with 5-fluorouracil and fluocinolone acetonide:," in Faber E. et al, editors: PSORIASIS: PROCEEDINGS OF THE THIRD INTERNATIONAL SYMPOSIUM, STANFORD UNIVERSITY, July 13-17 (1981). How to retain effectiveness while controlling local toxicity remained a challenging question.

SUMMARY OF THE INVENTION

This invention is a method for treating psoriasis comprising applying to the psoriatic lesion, an effective amount of a cytotoxic drug dispersed in a pharmaceutically acceptable vehicle containing a penetrating solvent for the drug. The drug is applied in a pulse of from 1 to 3 applications within a period of 48 hours to the skin area affected by the psoriasis without occlusion, and no further application is made for a period of from 3 to 30 days. This procedure is repeated until complete remission is effected.

Optimally, the penetrating solvent is free from toxic effects, such as AZONE or similar substituted azacycloalkyl-2-ones, tertiary amine oxides, and the like.

DETAILED DESCRIPTION OF THE INVENTION

I discovered that treatment of psoriasis using a weekly pulse dosing with topical applications of 5-fluorouracil with traditional vehicles under occlusion provided great improvement of the condition. Many patients had sustained remissions. Each week the patients had an average topical application pulse lasting 48 hours. I discovered that this weekly pulse dosing schedule eliminated the severe local toxicity seen with prior continuous daily dosing schedules. Dale Pearlman et al, *J.Am.Acad.Dermatol.* 15:1247-1252 (December, 1986).

While this therapy was quite effective, it took an average 15.7 weeks to achieve remission. I then discovered that the factor delaying remission was suboptimal tissue concentrations of 5-FU. By injecting 5-FU directly into the psoriatic tissue, I was able to achieve remission in an average of 4 weeks. Thus traditional vehicles, even under occlusion, are incapable of providing optimal transepidermal drug delivery.

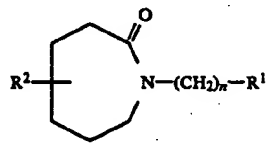
This invention is based on the discovery that with effective delivery of a cytotoxic agent through the stratum corneum, a superior therapeutic response is obtained if an effective amount drug is administered in one 48 hour pulse followed by a sustained pause of from 3 to 30 days and preferably from 4 to 14 days. During the 48 hour pulse period, the drug can be applied to the psoriatic lesion a sufficient number of times to achieve the desired tissue concentration, usually from 1 to 3 times being sufficient. Most optimally, a single application of drug is made to the lesion once a week. Effective remission is obtained, usually within 45 days, without significant inflammation or other evidence of severe damage to treated tissue.

An effective method for achieving this result is the topical application of an effective concentration of the cytotoxic agent together with a penetrating solvent such as AZONE, water-soluble tertiary amine oxide, DMSO or the like as a "pulse application" at an interval of from 3 to 30 and preferably at an interval of from 4 to 14 days. During the 48 hour pulse period, the drug-penetrating solvent preparation is applied for a sufficient number of times to achieve the desired drug concentration in the tissue. With most psoriatic lesions, the desired drug concentration can be achieved by from 1 to 3 applications of the drug-penetrating solvent composition.

In the method of this invention, a cytotoxic drug, in a vehicle containing a penetrating solvent, is applied topically to a skin area affected by psoriasis.

Suitable cytotoxic agents include 5-fluorouracil, colchicine, vinblastine sulfate, cyclophosphamide, azathioprine, cyclocytidine, azacytidine, azaserine, cisplatin, cycloheximide, mechlorethamine, cycloleucine, cytarabine, decarbazine, dactinomycin, dichloromethotrexate, emetrine hydrochloride, etoposide, quanazole, hydroxyurea, idoxuridine, mercaptopurine, methotrexate, methyl GAG (methylglyoxal bis(guanylhydrazone)), metoprine, pyrimethamine, scopolamine hydrobromide, thioquanine, thiotepa, vincristine sulface, and cyclosporin A, 5-fluorouracil being preferred.

Suitable penetrating solvents are solvents for the cytotoxic agent which will enhance percutaneous penetration of the drug. Solvents which have this property include dimethyl sulfoxide, dimethylacetamide, dimethyl formamide, and 1-methyl-2-pyrrolidone, and to a far lesser extent, propylene glycol. Preferred and superior solvents for this purpose are essentially free from adverse side effects and include substituted azacycloalkan-2-ones having from 5 to 7 carbons in the cycloalkyl group such as 1-dodecylazacycloheptan-2-one (AZONE) and other azacycloalkan-2-ones described in U.S. Pat. No. 3,989,816 (hereby incorporated by reference in its entirety) and represented by Formula I:



(I)

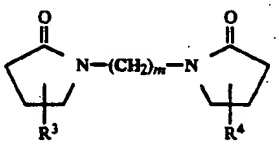
wherein

R^1 is a straight or branch chain alkyl group having from 1 to 18 carbons or aryl group having from 6 to 10 carbons;

R^2 is H or lower alkyl having from 1 to 4 carbons; and

n is an integer from 0 to 10.

Also included are N-bis-azacyclopentan-2-onyl alkanes described in U.S. Pat. No. 3,989,815 (hereby incorporated by reference in its entirety) and represented by Formula II:



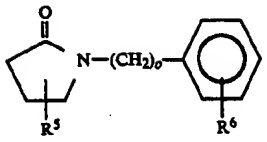
(II)

wherein

R^3 and R^4 are each H or a lower alkyl group having from 1 to 4 carbons; and

m is a positive integer of from 1 to 18.

Also included are 1-substituted azacyclopentan-2-ones described in U.S. Pat. No. 3,991,203 (hereby incorporated by reference in its entirety) and represented by Formula III:



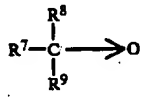
(III)

wherein

R_5 and R^6 are each H or lower alkyl having from 1 to 4 carbons; and

o is a positive integer from 0 to 10.

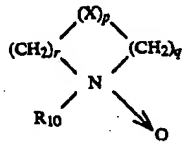
Also included are water-soluble tertiary amine oxides describe in U.S. Pat. No. 4,411,893 (hereby incorporated by reference in its entirety) and represented by Formulas IV and V:



(IV)

wherein

R^7, R^8 and R^9 are each saturated or unsaturated aliphatic radicals optionally containing ether or amide linkages and pendent hydroxyl groups, and the total number of carbon atoms of R^7, R^8 and R^9 does not exceed 28.



(V)

wherein

X is —O— or —N(R^{11})—;

R^{10} and R^{11} are each saturated or unsaturated aliphatic radicals having from 1 to 18 carbons and optionally containing ether or amide linkages and pendent hydroxyl groups; and

p is 0 or 1;

q is 2, 3 or 4; and

r is 2 or 3.

The topical formulation can be in the form of a lotion, cream, ointment, gel or solution, preferably a lotion, cream or solution containing a therapeutically effective amount of the cytotoxic drug and a sufficient proportion of penetrating solvent to solubilize the drug. Suitable drug concentrations will depend upon the choice of drug. Fluorouracil concentrations are from 0.001 to 5 weight percent and preferably from 1 to 5 weight percent.

For formulations with penetrating solvents of Formulas I, II and III, solutions or gels containing from 0.001 to 5 weight percent and preferably from 1 to 5 weight percent fluorouracil are preferred.

For formulations with penetrating agents such as the tertiary amine oxides of Formulas IV and V, the amine oxide and drug is incorporated into traditional lotions, gels and creams containing from 0.1 to 70 weight percent amine oxide, other traditional excipients, and water are preferred. These compositions can contain from 1 to 99 weight percent water.

A typical gel may contain, for example, one percent hydroxyethyl cellulose.

Typical lotion and cream formulations follows:

LOTION

Parts by Weight	Ingredient
5	polyoxylene-40-stearate
3	sorbitan monostearate
12	*mixture of lanolin, mineral oil and lanolin alcohol
6	cetyl alcohol
20	soybean oil
53.7	water
0.2	methyl paraben
0.1	propyl paraben

*AMERCOL BL (Amerchol Corp, Edison, N.J.)

CREAM

Parts by Weight	Ingredient
3	polyoxyethylene-4-stearate
2.5	sorbitan monostearate
10	soybean oil
10	*mixture of lanolin, mineral oil and lanolin alcohol
1	cetyl alcohol
73.2	water
0.2	methyl paraben
0.1	propyl paraben

*AMERCOL BL (Amerchol Corp, Edison, N.J.)

The composition containing the cytotoxic agent and penetrating solvent are applied to the skin are having the psoriasis in a quantity sufficient to wet or to cover to surface.

A critical aspect of this invention is the interval between pulses. In contrast to the previous methods of applying these agents, in penetrating solvents, they are applied according to this invention in single pulses at intervals of from 3 to 30 days and preferably at intervals of from 4 to 14 days. The procedure is repeated until the condition disappears. A total of from 1 to 6 application pulses is usually sufficient with fluorouracil.

When applied in accordance with this invention, the psoriasis disappears without extensive inflammation (erythma) of the treated skin surface. For patients with particular sensitivity to the cytotoxic agent, applications at longer intervals within the suggested range is suggested. If erythema begins to appear, the intervals should be lengthened until all signs of significant skin irritation disappear.

Occlusion is usually not necessary with the method of this invention. In a situation where the use of occlusion is believed necessary, the intervals between application times should be lengthened since cytotoxic agent damage to treated cells is usually increased by occlusive dressings.

Because the patient response will vary from patient to patient, the following examples include procedures for optimizing the parameters of drug concentration, number of applications per pulse, and the intervals between pulses. The preparations are applied initially once a week to the psoriatic lesions in an amount sufficient to moisten the surface. Depending upon the patient's response to the therapy, the physician can elect to continue the therapy in the same manner if progress is satisfactory or elect to vary any of the parameters. The concentration of drug and penetration agent can be varied until the desired amount of drug concentration in the tissue is obtained. Initially, one application per pulse can be used, and the period of exposure of the lesions to

the drug is selected to achieve the desired amount of drug concentration in the tissue. The number of applications per pulse and the duration of the interval between pulses is determined by the response of the psoriasis to treatment and the time required for the treated skin to recover from exposure to the drug, timed to minimize local toxicity.

Once remission is achieved, physicians may choose two courses of treatment during remission. Preferably, no therapy is applied until relapse occurs. Then an appropriate therapy schedule is reinstated. Alternatively, in order to maintain a remission, maintenance therapy may be selected, applying drug/penetrating agent compositions delivering the lowest effective dose of drug with the longest intervals between applications still providing effective remission.

This invention is further illustrated by the following specific but non-limiting examples. In the examples, temperatures are given in degrees Centigrade and concentrations are given as weight percents, unless otherwise indicated. Examples constructively reduced to practice in filing this application are presented in the present tense, and examples describing procedures carried out in the laboratory or clinic are set forth in the past tense.

EXAMPLE 1

Titration of Drug Treatment Parameters

Solution A is prepared comprising 1 wt. % 5-FU, 2 wt. % AZONE, 50 wt % propylene glycol and the remainder, sterile, deionized water.

Solution A is applied to psoriasis of the knee once weekly in an amount sufficient to moisten the surface. If, at the end of two weeks, the response to the treatment is less than desired, a more concentrated solution (Solution B) is prepared containing 5 wt. % 5-FU, 2 wt. % AZONE, 50 wt. % propylene glycol and the remainder sterile, deionized water.

If the progress is still unsatisfactory, the application regiment is modified. Two applications of Solution B are applied in a pulse of two applications 12 hours apart. The interval between pulses is left unchanged. If the rate of progress is satisfactory, and no local toxicity is observed, the regimen is repeated with this concentration until complete remission is achieved.

EXAMPLE 2

Optimizing Pulse Timing Cream Composition

Cream A is prepared containing 5 wt. % 5-FU, 40 wt. % 1-benzylazacyclopentan-2-one and the remainder inert excipients which provide a stable cream composition (AMERCOL BL, described above).

Cream A is applied once weekly to psoriasis on the elbows in an amount sufficient to moisten the surface. If after 2 weeks the rate of progress is satisfactory but there is evidence of mild, local toxicity, a rest period of no therapy is instituted for one week to allow recovery from the toxicity. Treatment is then reinstated changing the interval between pulses to 2 weeks, leaving the formula and number of applications unchanged. If after 2 weeks, the rate of recovery is satisfactory, and no local toxicity is observed, the program is continued until remission is achieved.

EXAMPLE 3

Optimizing Lotion Composition

Lotion A is prepared with the following composition: 5-FU, 1 wt. %; N-bis-1,6(azacyclopentan-2-onyl)hexane, 20 wt %.; cetyl alcohol, 15 wt. %; propylene glycol, 10 wt. %; sodium lauryl sulfate, 15 wt. %; and sterile, deionized water qs. ad.

The patient begins treatment with the lotion applied once a week in an amount sufficient to moisten the surface of the psoriatic lesion. If after 2 weeks, the rate response is inadequate though no local toxicity is observed, Lotion B is prepared having the following ingredients: 5-FU, 5 wt. %; N-bis-1,6(azacyclopentan-2-onyl)hexane, 20 wt %.; cetyl alcohol, 15 wt. %; propylene glycol, 10 wt. %; sodium lauryl sulfate, 15 wt. %; and sterile, deionized water qs. ad. Lotion B is applied once a week in an amount sufficient to moisten the surface.

If after 2 weeks, the rate of response is still inadequate without local toxicity, the number of applications per pulse is increased to 3 separate applications with a separation of 12 hrs between applications, with no change in formula or interval between pulse doses. If after 2 weeks, the rate of progress is improved, but slight local toxicity is observed, the interval between pulses is increased to 2 weeks with the other parameters remaining unchanged.

If after two weeks, the rate of progress is adequate and no local toxicity is observed, the therapy regimen in repeated without change until complete remission occurs.

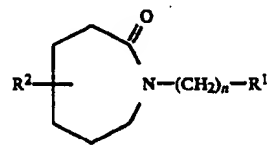
I claim:

1. A method for treating psoriasis consisting essentially of applying a therapeutically sufficient quantity of a composition consisting essentially of 5-fluorouracil dissolved in a penetration enhancing agent to a psoriatic lesion until remission occurs, the composition being applied in one or more pulses at about one week intervals, each pulse comprising applying to the lesion one or more times over a period of up to 48 hours, an amount of the composition sufficient to wet the lesion.

2. The method of claim 1 wherein the penetration enhancing agent includes propylene glycol.

3. The method of claim 2 wherein a solution of from 0.001 to 5 wt. % 5-fluororacil in propylene glycol is applied to psoriatic lesion.

4. The method of claim 1 wherein the penetration enhancing agent includes compound of Formula I, II or III:



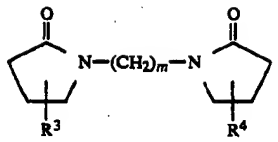
(I)

wherein

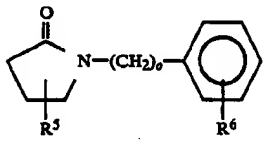
R^1 is a straight or branch chain alkyl group having from 1 to 18 carbons or aryl group having from 6 to 10 carbons;

R^2 is hydrogen or lower alkyl having from 1 to 4 carbons; and

n is an integer from 0 to 10;


(II)

wherein
R^3 and R^4 are each hydrogen or a lower alkyl group having from 3 to 4 carbons; and
m is an integer from 1 to 18; or


(III)

wherein
R^5 and R^6 are each hydrogen or lower alkyl having from 1 to 4 carbons; and
o is an integer from 0 to 10.

5. The method of claim 4 wherein the penetration enhancing agent is a compound of Formula I.

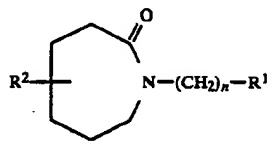
6. The method of claim 5 wherein the penetration enhancing agent is 1-dodecylazacycloheptan-2-one.

7. A method for treating psoriasis consisting essentially of applying a therapeutically sufficient quantity of a composition consisting essentially of 5-fluorouracil dissolved in a penetration enhancing agent to a psoriatic lesion until remission occurs, the composition being applied in one or more pulses at from 3 to 30 day intervals, each pulse comprising applying the composition to the lesion one or more times over a period of up to 48 hours.

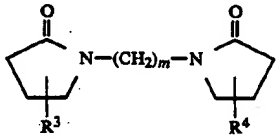
8. The method of claim 7 wherein the penetration enhancing agent includes propylene glycol.

9. The method of claim 8 wherein a solution of from 0.001 to 5 wt. % 5-fluorouracil in propylene glycol is applied to the psoriatic lesion.

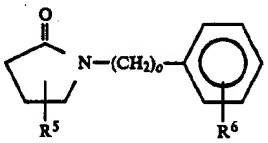
10. The method of claim 7 wherein the penetration enhancing agent includes a compound of Formula I, II or III:


(I)

wherein
R^1 is a straight or branch chain alkyl group having from 1 to 18 carbons or aryl group having from 6 to 10 carbons;
R^2 is hydrogen or lower alkyl having from 1 to 4 carbons; and
n is an integer from 0 to 10;


(II)

wherein
R^3 and R^4 are each hydrogen or a lower alkyl group having from 3 to 4 carbons; and
m is an integer from 1 to 18; or


(III)

wherein
R^5 and R^6 are each hydrogen or lower alkyl having from 1 to 4 carbons; and
o is an integer from 0 to 10.

* * * * *

United States Patent [19]

Hill et al.

[11] **4,233,295**

[45] **Nov. 11, 1980**

[54] **CORTICOSTEROID FORMULATIONS CONTAINING SEBACATE CARRIER**

[75] Inventors: **John A. Hill, New Brunswick; Yu-chang J. Wang; Thomas M. Wong, both of North Brunswick, all of N.J.**

[73] Assignee: **E. R. Squibb & Sons, Inc., Princeton, N.J.**

[21] Appl. No.: **43,989**

[22] Filed: **May 31, 1979**

[51] Int. Cl.[3] **A01N 45/00; A61K 31/56**

[52] U.S. Cl. **424/238**

[58] Field of Search 424/238

[56] **References Cited**

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4,082,881	4/1978	Chen et al.	424/238

Primary Examiner—Elbert L. Roberts

Attorney, Agent, or Firm—Lawrence S. Levinson; Burton Rodney

[57] **ABSTRACT**

Corticosteroid formulations in the form of creams, lotions or ointments are provided which are used as anti-inflammatory agents, wherein the corticosteroid, such as halcinonide (21-chloro-9-fluoro-11β-hydroxy-16α,17-[(1-methylethylidene)-bis(oxy)]pregn-4-ene-3,20-dione) is dissolved in a sebacate carrier, such as dibutyl sebacate.

16 Claims, No Drawings

CORTICOSTEROID FORMULATIONS CONTAINING SEBACATE CARRIER

DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical formulations which include a dialkyl sebacate, such as dibutyl sebacate or diisopropyl sebacate as a vehicle for the pharmaceutical.

Topical corticosteroid formulations are extensively employed in the treatment of skin disorders, such as dermatitis. To be therapeutically effective, the active ingredient preferably should be in a molecular dispersion to facilitate desired percutaneous absorption which is particularly important in achieving a therapeutic response for the management of psoriasis. Unfortunately, many of the desirable steroids are insoluble in water and even less soluble in hydrocarbon vehicles such as mineral oil, petrolatum or polyethylene gelled mineral oil.

Various organic solvents and solubilizers have been found to be good solvents for steroids. However, many of such solvents have been found to be unsuitable for commercial application for reasons such as their high volatility and low boiling points, their disagreeable odor, their "paint removing" property, or their undesirable skin reaction. Furthermore, various water-soluble or water-dispersible emulsifiers and oil liquids or emollients have been suggested for use in preparing ointments, gels, creams and lotions. However, because of the undesirably low solubility of the steroid in many such vehicles, higher levels of these materials in topical products are required thereby increasing their cost and also adversely affecting their cosmetic elegance.

Accordingly, in view of the above considerations, it is seen that a need exists for a suitable vehicle capable of solubilizing a sufficient amount of the steroid so that it may be employed in a topical formulation, while being dermatologically beneficial, stable, and pharmaceutically acceptable.

In accordance with the present invention, it has now been found that sebacates, such as dialkyl sebacates, wherein alkyl contains 1 to 10 carbons, for example, dibutyl sebacate and diisopropyl sebacate, are excellent vehicles for corticosteroids.

The active ingredient employed in the formulations of the invention will preferably comprise a steroid which will be present in an amount of from about 0.001 to about 3% by weight, and preferably from about 0.025 to about 0.2% based on the total weight of the composition, depending upon the type of steroid employed and its solubility in the sebacate containing vehicle.

Exemplary of the steroids contemplated are the acetonide derivatives of steroids of the pregnane series described in U.S. Pat. Nos. 3,048,581 and 3,937,720. Included within the steroids described by the former patent is halcinonide In addition, the sebacate may be employed to dissolve steroids disclosed in U.S. Pat. Nos. 3,976,637, 3,979,417, 3,994,935, 4,018,757, 4,116,978, 4,018,774, 4,091,036, 4,094,840, 4,133,811 and 4,146,538, U.S. application Ser. No. 919,006, filed June 26, 1978, now U.S. Pat. No. 4,160,772 and U.S. application Ser. No. 919,020, filed June 26, 1978, now U.S. Pat. No. 4,164,504.

In preferred embodiments, dibutyl sebacate or diisopropyl sebacate are employed to dissolve halcinonide, 21-(acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4dieno[16α,17-b]-naphthalene-3,20-dione, 21-chloro-9-fluoro-1',2'-3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,-17-b]naphthalene-3,20-dione, (11β,16α)-9-fluoro-1',2',3',4'-tetrahydro-11-hydroxy-3,20-dioxopregna-1,4-dieno[16α,17-b]naphthalen-21-oic acid, 1-methylethyl ester, or (11β,16α)-9-fluoro-11-hydroxy-3,20-dioxopregna-1,4-dieno[16,17-d]cyclohexen-21-oic acid, 1-methylethyl ester. It is emphasized that these steroids are meant to be exemplary only and it is not meant to limit this invention to use with any particular steroid or group of topically active anti-inflammatory steroids.

The sebacate will be present in the compositions of the invention in amounts within the range of from about 5 to about 95% and more depending upon the type of pharmaceutical composition and the active ingredient contained therein.

The formulations employing the sebacate vehicle in accordance with the present invention may take the form of a hydrophobic base such as an ointment (non-aqueous) or gel, as well as a cream, lotion, and liquid including parenterals, nose drops, ear drops and the like.

The lotion or cream includes the sebacate as the oil phase. The lotions and creams of the invention will include the active ingredient "all-in-solution" so that substantially no active ingredient crystallizes out at room temperature.

With regard to the cream formulations of the invention where the steroid is to be all-in-solution, the cream will contain from about 0.005 to about 0.6% and preferably from about 0.025 to about 0.2% by weight of the active ingredient based on the weight of the entire cream formulation, and from about 5 to about 75% and preferably from about 10 to about 50% by weight of the sebacate based on the weight of the entire cream formulation and depending upon the solubility of the particular active ingredient in the particular sebacate employed. The all-in-solution cream formulation will include substantially all of the active ingredient in the oily sebacate phase.

Where present, an anti-whitening agent or anti-foaming agent will comprise a separate oil phase and will be present in an amount within the range of from about 0.2 to about 3% and preferably from about 0.5 to about 1.5% by weight based on the entire cream formulation. An antioxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.1% and preferably from about 0.01 to about 0.05% by weight based on the entire cream formulation.

The aqueous phase of the all-in-solution cream formulation may contain a glycol type preservative such as propylene glycol in an amount within the range of from about 2 to about 50% and preferably from about 4 to 40% by weight of the entire cream formulation and/or a paraben or other conventional type preservative such as methyl and/or propyl paraben in an amount ranging from about 0.05 to about 0.5%, and purified water in an amount within the range of from about 30 to about 70% by weight and preferably from about 35 to about 65% by weight of the entire cream formulation.

With regard to the lotion formulation of the invention where the steroid is to be all-in-solution, the lotion will contain from about 0.005 to about 0.6% and preferably from about 0.02 to about 0.05% by weight of the active ingredient based on the weight of the entire lotion formulation, and from about 5 to about 75% and preferably from about 10 to about 50% by weight of the sebacate based on the weight of the entire lotion formulation,

depending upon the solubility of the particular ingredient in the sebacate.

The above lotions or creams may contain from abut 5 to about 14% and preferably from about 8 to about 12% by weight emulsifier-thickener (such as, cetyl alcohol) based on the weight of the entire lotion formulation.

In general, emulsifier-thickeners suitable for use herein may comprise ethers of polyethylene glycol and fatty alcohols, such as, Promulgen, Robinson Wagner Co., which contains some unreacted cetyl and stearyl alcohol, and other non-ionic emulsifying waxes such as Polawax, Croda Co.

The same emulsifier-thickener used in the formulations of the invention may also be obtained by substituting the above-mentioned emulsifying waxes with a mixture of polyoxyethylene (20) stearyl alcohol ether (BRIJ 78, ICI) or polyoxyethylene (20) cetyl alcohol ether (BRIJ 58, ICI) with cetyl or stearyl alcohol. The ratio of the BRIJ or a mixture of the two BRIJ with the fatty alcohol or a mixture of the two alcohols should be within the range of from about 0.6 to about 3.5, preferably from about 1 to about 3.

Another emulsifier system suitable for use in the invention comprises a combination of glyceryl monostearate with polyoxyethylene sorbitan palmitate or stearate and stearyl alcohol. For example, a cream or lotion containing 0.025% by weight halcinonide in dibutyl sebacate (5–50%), an oil-in-water cream, can be made with glyceryl monostearate (1–8%), cetyl alcohol (2–6%) and Tween 60 (polyoxyethylene sorbitan monostearate 2–7.1%).

It will also be appreciated that two or more materials may be employed to provide the emulsifying function and the thickening function. Thus, examples of emulsifying agents suitable for use herein include propylene glycol monostearate, as well as the non-ionic polyoxyalkylene derivatives of hexitol anhydride partial long chain fatty acid esters, e.g., the polyoxyalkylene derivative of sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate or sorbitan trioleate. These emulsifying agents are commercially available as Tween 20, 21, 40, 60, 65, 80, 81 and 85.

Thickeners suitable for use in combination with the above emulsifying agents include those conveniently employed in topical creams, such as, for example, monoglycerides and fatty alcohols, fatty acid esters of alcohols having from about 3 to about 16 carbon atoms. Examples of suitable monoglycerides are glyceryl monostearate and glyceryl monopalmitate. Examples of fatty alcohols are cetyl alcohol and stearyl alcohol. Examples of suitable esters are myristyl stearate and cetyl stearate. The monoglyceride also functions as an auxiliary emulsifier. Other emollients or oleaginous materials which may be employed include petrolatum, glyceryl monooleate, myristyl alcohol and isopropyl palmitate.

A second oil phase may also optionally include an anti-whitening agent or anti-foaming agent, such as silicone fluid, in an amount within the range of from about 0.2 to about 3% and preferably from about 0.5 to about 1.5% by weight based on the entire lotion formulation. An anti-oxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.1% and preferably from about 0.01 to about 0.05% by weight based on the entire lotion formulation.

The aqueous phase of the all-in-solution lotion formulation may contain a glycol-type preservative, such as propylene glycol or 1,3-butylene glycol, in an amount within the range of from about 5 to about 50% and preferably from about 12 to about 40% by weight of the entire lotion formulation, and/or parabens (p-hydroxy benzoates) or other conventional type preservative in an amount ranging from about 0.05 to about 0.5%, and purified water in an amount within the range of from about 50 to about 90% by weight and preferably from about 60 to about 85% by weight of the entire lotion formulation.

Where the active ingredient is to be employed in parenteral solutions, the sebacate vehicle will be present in amounts ranging from about 80 to about 99%, and preferably from about 85 to about 98%; the concentration of the active ingredient will vary depending upon the type employed and will range from about 0.01 to about 2.5% by weight. A 1 to 5% ethanol solution may be used to enhance clarity of the product.

When the formulation of the invention is in the form of nose drops or ear drops, the sebacate vehicle will be present in amounts ranging from about 80 to about 99% and preferably from about 85 to about 98% by weight while the active ingredient will vary depending upon the type used.

With regard to specific steroid formulations, where halcinonide is employed in all-in-solution creams or lotions, the sebacate vehicle will be preferably employed in an amount within the range of from about 30 to about 70% by weight and more preferably within the range of from about 40 to about 60% by weight, while the steroid will be present in amounts ranging from about 0.02 to about 0.2% by weight.

Where 21-(acetyloxy)-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione is employed in all-in-solution creams or lotions, the sebacate vehicle will be preferably employed in an amount within the range of from about 5 to about 50% by weight and more preferably within the range of from about 5 to about 30% by weight while the steroid will be employed in amounts ranging from about 0.02 to about 0.2% by weight.

Where other steroids are employed in a cream or lotion, the sebacate vehicle will be preferably employed in amounts within the range of from about 5 to about 75% by weight and preferably from about 10 to about 50% by weight while the active steroid may be employed in amounts within the range of from about 0.001 to about 0.2% by weight.

The hydrophobic formulations of the invention which include non-aqueous ointments, gels and the like, comprise a steroid as described herein, a sebacate vehicle and oleaginous material, and optionally a wax and/or antioxidant.

The oleaginous material will generally be present in an amount within the range of from about 25 to about 99% by weight, and preferably from about 50 to about 90% by weight.

The ointments of the invention may include the active steroid ingredient solubilized in the continuous sebacate phase.

The ointment will contain from about 0.001 to about 2%, and preferably from about 0.025 to about 0.2% by weight of the steroid ingredient, and from about 5 to about 75% and preferably from about 5 to about 65% by weight of the sebacate based on the weight of the entire ointment formulation and depending upon the solubility of the particular active ingredient in the particular sebacate employed. The all-in-solution ointment

formulation (exclusive of the gel) will also include, in addition to the active ingredient and sebacate, from about 25 to about 95% and preferably from about 85 to about 95% by weight of oleaginous material based on the weight of the entire formulation. The formulation may also optionally include an opacifying agent, such as titanium dioxide, serving as indicator for homogeneity of dispersion, in an amount within the range of from about 0.2 to about 1% and preferably from about 0.3 to about 0.8% by weight based on the entire formulation. An antioxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.1% and preferably from about 0.01 to about 0.05% by weight based on the entire formulation.

Examples of oleaginous material suitable for use herein are petrolatum, other sebacate miscible or immiscible oily material and mineral oil thickened or gelled with polyethylene, or high molecular weight paraffin waxes or mono and diglycerides of fatty acids gelled with high molecular weight fatty acids and/or polyamide complex of hydroxystearate. Petrolatum (petroleum jelly) is a purified mixture of semisolid hydrocarbons from petroleum having a melting point of from about 45° to about 65° C., preferably from about 50° to about 60° C. When the mixture of active ingredient and sebacate is mechanically dispersed in the oleaginous material, the mixture may be gelled by polyethylene as disclosed in U.S. Pat. Nos. 2,627,938, 2,628,187, 2,628,205 and 3,733,403. The disclosures of the foregoing patents are incorporated herein by reference.

The all-in-solution ointment may simply be prepared by dissolving the active ingredient in the sebacate with gentle heat not over 90° C., cooling to room temperature and then incorporating the same into the oleaginous material by slow mixing until homogeneous. If the steroid is not completely dissolved in the sebacate, then another vehicle such as polyethylene glycol, propylene glycol, butylene glycol, propylene carbonate or other known solvents for steroids may be used to dissolve the undissolved portion of the steroid. Thereafter, the steroid-vehicle combination may be dispersed with the sebacate portion.

The gel formulation of the invention is preferably in the form of a lipophilic gel, and will contain from about 0.005 to about 3%, and preferably from about 0.025 to about 0.5% by weight of the active steroid based on the weight of the entire formulation, and from about 0.5 to about 20% and preferably from about 1 to about 10% by weight of the sebacate based on the weight of the entire formulation, depending upon the solubility of the particular active steroid. The formulation may also optionally include a surfactant, such as Span 65 (sorbitan tristearate), as well as Span 60 (sorbitan monostearate), Span 40 (sorbitan monopalmitate), butylene glycol distearate in amounts up to about 8% by weight based on the entire formulation. An antioxidant, such as butylated hydroxyanisole or butylated hydroxytoluene may also optionally be included in amounts up to about 0.1% and preferably up to about 0.05% by weight based on the entire formulation.

In the non-aqueous gel formulation of the invention, various gelling agents may be employed to gel the sebacate, such as waxes, for example, high molecular weight paraffin wax (Paraflint RG), propylene glycol isostearate (Emery 2389A), polyamide complex of hydroxystearate (Acrowax, Glyco), carnauba wax, white wax, ozokerite and/or candelilla wax.

With regard to specific steroid ointment or gel formulations, where halcinonide is employed in all-in-solution ointments, the sebacate vehicle will be preferably employed in an amount within the range of from about 10 to about 90% by weight and more preferably within the range of from about 25 to about 65% by weight, while the steroid will be employed in amounts ranging from about 0.001 to about 1% by weight.

Where 21-(acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione is employed in all-in-solution ointments the sebacate vehicle will be preferably employed in an amount within the range of from about 10 to about 90% by weight and more preferably within the range of from about 25 to about 65% by weight while the steroid will be employed in amounts ranging from about 0.001 to about 1% by weight.

In the case of ointments and lipophilic gels where the formulation is substantially free of water, the active ingredient will be dissolved in the sebacate vehicle and, in part, in other vehicles which may be employed as described hereinbefore.

The cream, lotion or ointiment may also contain an antioxidant such as butylated hydroxytoluene, butylated hydroxyanisole and the like for protecting the active ingredient against oxidation.

Examples of preferred dibutyl sebacate or diisopropyl sebacate vehicles in accordance with the present invention include, but are not limited to, the following.

Aqueous Cream for Moderately Insoluble Steroids	Parts by Weight
Dibutyl of Diisopropyl sebacate	15 to 25
Polysorbate 60	2 to 8
Glyceryl stearate	3 to 10
White wax	1 to 5
Preservative (propylene glycol)	6 to 15
Anti-foam agent (dimethicone)	0 to 2
Water q.s to make	100 parts

Aqueous Cream for Insoluble Steroids	Parts by Weight
Dibutyl or Diisopropyl sebacate	25 to 60
Glyceryl stearate	1 to 5
White wax	3 to 7
Promulgen D (cetearyl alcohol and ceteareth-20), Robinson-Wagner	4 to 10
Dimethicone	0 to 2
Propylene glycol	5 to 20
Water q.s. to make	100 parts

Anhydrous Gels	Parts by Weight		
	1	2	3
Dibutyl or diisopropyl sebacate	85 to 95	80 to 92	65 to 75
Carnauba wax	15 to 50		
Polyethylene		20 to 8	10 to 15
Mineral oil			15 to 20

Examples of preferred steroid formulations in accordance with the present invention include, but are not limited to, the following:

Halcinonide Topical Cream, 0.025%	Ranges
Halcinonide, micronized	0.022–0.03 gm.
Dibutyl or diisopropyl sebacate	6–10 gm.
Polysorbate 60	2–8 gm.

-continued

or	or
Promulgen, Type D (Cetearyl alcohol & Ceteareth-20),	
Robinson-Wagner	4–10 gm.
Glyceryl stearate	1–5 gm.
White wax	3–7 gm.
Propylene glycol	5–15 gm.
Dimethicone 350	0–2 gm.
Purified water, q.s.	100.0 gm.

Halcinonide Topical Cream, 0.1%

	Ranges
Halcinonide, micronized	0.09–0.11 gm.
Dibutyl or Diisopropyl sebacate	25–35 gm.
Polysorbate 60	2–8 gm.
or	or
Promulgen, Type D (Cetearyl alcohol & Ceteareth-20),	
Robinson-Wagner	4–10 gm.
Glyceryl monostearate	1–5 gm.
White wax	3–7 gm.
Propylene glycol	5–15 gm.
Dimethicone 350	0–2 gm.
Purified water, q.s.	100.0 gm.

Topical Cream Containing 0.025% 21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione

Steroid, micronized	0.02–0.03 gm.
Dibutyl or Diisopropyl sebacate	3–10 gm.
Polysorbate 60	2–8 gm.
or	or
Promulgen D	4–10 gm.
Glyceryl monostearate	1–5 gm.
White wax	3–7 gm.
Propylene glycol	5–15 gm.
Dimethicone 350	0–2 gm.
Purified water 0.50	100.0 gm.

Topical Cream Containing 0.1% 21-(Acetyloxy)-9-fluoro-1', 2', 3', 4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α-,17-b]naphthalene-3,20-dione

	Ranges
Steroid, micronized	0.09–0.11 gm.
Dibutyl or Diisopropyl sebacate	15–25 gm.
Polysorbate 60	2–8 gm.
or	or
Promulgen, Type D (Cetearyl alcohol & Ceteareth-20),	
Robinson-Wagner	4–10 gm.
Glyceryl monostearate	1–5 gm.
White wax	3–7 gm.
Propylene glycol	5–15 gm.
Dimethicone 350	0–2 gm.
Purified water, q.s.	100.0 gm.

Halcinonide Lotion 0.025%

Halcinonide, micronized	0.02–0.03 gm.
Dibutyl or Diisopropyl sebacate	3–10 gm.
Polysorbate 60	2–8 gm.
Sodium carboxymethyl cellulose	2–8 gm.
Cetyl alcohol	1–3 gm.
Propylene glycol	5–15 gm.
Purified water, q.s.	100.0 gm.

Lotion Containing 0.025% 21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione

	Ranges
Steroid, micronized	0.02–0.03 gm.
Dibutyl or Diisopropyl sebacate	3–10 gm.
Polysorbate 60	2–8 gm.
Sodium carboxymethyl cellulose	2–8 gm.
Cetyl alcohol	1–3 gm.
Methyl paraben	0.1–0.5 gm.
Propyl paraben	0.01–0.05 gm.
Purified water, q.s.	100.0 gm.

Intramuscular Injection Containing 4% 21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione

-continued

Steroid	4 gm.
Benzyl alcohol	0.5–2.5 gm.
Dibutyl sebacate sufficient to make	100 ml.

The following examples illustrate preferred embodiments of the present invention without, however, limiting the same thereto. All temperatures are expressed in degrees Centigrade.

EXAMPLE 1

Cream Containing 0.025% 21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno-[16α,17-b]naphthalene-3,20-dione (all-in-solution)

Steroid, micronized	0.025 gm.
Dibutyl sebacate	5 gm.
Glyceryl stearate	4 gm.
White wax	4 gm.
Promulgen, Type D (PEG fatty alcohol ether)-Cetearyl alcohol & Ceteareth-20 (Robinson-Wagner)	7 gm.
Propylene glycol	15 gm.
Dimethicone 350	1 gm.
Purified water, sufficient to make	100.0 gm.

The steroid is dissolved in dibutyl sebacate with gentle heat not over 90° C. The glyceryl stearate, white wax, Dimethicone 350 and Promulgen are melted together and heated to 75°–80° C. and then mixed with the above steroid solution and the propylene glycol. The resulting mixture is added to hot 75°–80° C. purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48° C. Sufficient hot (48°–50° C.) purified water is then added to make 100 gm. Mixing is then continued at a slow rate during the congealing stage until the cream reaches room temperature.

EXAMPLE 2

Halcinonide Cream 0.025%

Halcinonide, micronized	0.025 gm.
Dibutyl sebacate	7 gm.
Glyceryl stearate	4 gm.
White wax	4 gm.
Promulgen, Type D (PEG fatty alcohol ether)-Cetearyl alcohol & Ceteareth-20 (Robinson-Wagner)	7 gm.
Propylene glycol	15 gm.
Dimethicone 350	1 gm.
Purified water, sufficient to make	100.0 gm.

The above cream is prepared employing the procedure of Example 1.

EXAMPLE 3

Halcinonide Cream 0.1%

Halcinonide, micronized	0.1 gm.
Dibutyl sebacate	30 gm.
Glyceryl stearate	4 gm.
White wax	4 gm.
Promulgen, Type D (PEG fatty alcohol ether)-Cetearyl alcohol & Ceteareth-20 (Robinson-Wagner)	9 gm.
Propylene glycol	11 gm.

-continued

Halcinonide Cream 0.1%	
Dimethicone 350	1 gm.
Purified water, sufficient to make	100.0 gm.

The above cream is prepared employing the procedure described in Example 1.

EXAMPLE 4

Cream Containing 0.1% 21-(Acetyloxy-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16β,17-b]-naphthalene-3,20-dione	
Steroid	0.1 gm.
Dibutyl sebacate	18 gm.
Glyceryl stearate	4 gm.
White wax	4 gm.
Promulgen, Type D (PEG fatty alcohol ether)-Cetearyl alcohol & Ceteareth-20 (Robinson-Wagner)	9 gm.
Propylene glycol	11 gm.
Dimethicone 350	1 gm.
Purified water, sufficient to make	100.0 gm.

The above cream is prepared as described in Example 1.

EXAMPLE 5

Halcinonide Lotion 0.025%	
Halcinonide, micronized	0.025 gm.
Dibutyl sebacate	7 gm.
Polysorbate 60	5 gm.
Sodium carboxymethyl cellulose	5 gm.
Cetyl alcohol	2 gm.
Methylparaben	0.3 gm.
Propylparaben	0.03 gm.
Purified water, q.s.	100 gm.

The steroid and parabens are dissolved in dibutyl sebacate with gentle heat, not over 90° C. and melted together and Polysorbate 60 and cetyl alcohol added, while maintaining the temperature at 75°–80° C. Water is heated to 80° C. to dissolve the sodium carboxymethyl cellulose forming an aqueous phase which is added with vigorous agitation to the oil phase to emulsify. Agitation is continued until the temperature drops down to 48° C. Sufficient 50° C. water is added to make 100 gm. Mixing is continued at a slow rate to congeal the mixture, until the lotion drops down to room temperature.

EXAMPLE 6

Lotion Containing 0.025% 21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α-17-b]naphthalene-3,20-dione	
Steroid, micronized	0.025 gm.
Dibutyl sebacate	5 gm.
Polysorbate 60	5 gm.
Sodium carboxymethyl cellulose	5 gm.
Cetyl alcohol	2 gm.
Methylparaben	0.3 gm.
Propylparaben	0.03 gm.
Purified water, q.s.	100 gm.

The above lotion is prepared employing the procedure of Example 5.

EXAMPLE 7

Intramuscular Injection Containing 4% 21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione	
Steroid	4 gm.
Benzyl alcohol	2 gm.
Dibutyl sebacate sufficient to make	100 gm.

The above injectable is prepared by simply mixing and sterilizing the above ingredients.

EXAMPLE 8

Cream Containing 0.1% 21-Chloro-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione	
Steroid	0.1 gm.
Diisopropyl sebacate	35 gm.
Glyceryl stearate	5 gm.
White wax	4 gm.
Promulgen	7 gm.
Dimethicone	1 gm.
Propylene glycol	12 gm.
Purified water, q.s. to make	100 gm.

The above cream is prepared employing procedures similar to that described in Example 1.

EXAMPLE 9

Cream Containing 0.2% (11β,16α)-9-Fluoro,1',2',3',4'-tetrahydro-11-hydroxy-3,20-dioxopregna-1,4-dieno-[16α,17-b]naphthalen-21-oic acid, 1-methylethyl ester	
Steroid	0.2 gm.
Dibutyl sebacate	15 gm.
Glyceryl stearate	5 gm.
White wax	4 gm.
Polysorbate 60	5 gm.
Dimethicone	1 gm.
Propylene glycol	15 gm.
Purified water q.s. to	100 gm.

The above cream is prepared employing procedures as described in Example 1.

EXAMPLE 10

Ointment, 0.025% (all-in-solution)	
Halcinonide, micronized	0.025 gm.
(a) Dibutyl sebacate	50 gm.
(b) Mineral Oil	44 gm.
(a) and (b) gelled with polyethylene)	5 gm.
Titanium dioxide	0.5 gm.

The steroid is dissolved in dibutyl sebacate, and mineral oil and polyethylene are added to the solution with gentle heat not over 90° C. The mixture is heated to 120° C. until homogeneous. The mixture is shock cooled to room temperature and titanium dioxide is dispersed homogeneously therein.

EXAMPLE 11

Lipophilic gel, 0.025% (all-in-solution)	
Halcinonide, micronized	0.025 gm.
Dibutyl sebacate	92 gm.

-continued

Lipophilic gel, 0.025% (all-in-solution)	
Carnauba wax	8 gm.

The steroid is dissolved in dibutyl sebacate by gentle heat (70° C.). The carnauba wax is added, allowed to dissolve, and the melted mass shockcooled by pouring the solution onto a cold surface.

The gel obtained is a smooth, glossy semisolid ointment-like gel.

What is claimed is:

1. A steroid composition in the form of an ointment, gel, lotion, cream or solution which is useful in treating dermatitis, consisting essentially of an effective amount of from about 0.001 to about 3% by weight of a corticosteroid and a dialkyl sebacate in an amount of from about 5 to about 75% by weight of the composition, the corticosteroid being dissolved in the dialkyl sebacate.

2. The steroid composition as defined in claim 1 wherein said sebacate vehicle is present in an amount within the range of from about 5 to about 95% by weight of the composition.

3. The steroid composition as defined in claim 1 in the form of an ointment, gel, lotion, cream or solution.

4. The steroid composition as defined in claim 1 wherein said sebacate is dibutyl sebacate.

5. The steroid composition as defined in claim 1 wherein said sebacate is diisopropyl sebacate.

6. The steroid composition as defined in claim 1 wherein said steroid is halcinonide or triamcinolone acetonide.

7. The steroid composition as defined in claim 3 in the form of a cream or lotion wherein said steroid is present in an amount within the range of from about 0.005 to about 0.6% by weight of the composition, said sebacate vehicle is present in an amount within the range of from about 5 to about 75% by weight of the composition.

8. The steroid composition as defined in claim 7 and further including an emulsifier-thickener present in an amount within the range of from about 1 to about 14% by weight of the composition, a preservative present in an amount within the range of from about 0.05% to about 50% by weight of the composition, and water present in an amount within the range of from 30 to about 90% by weight of the composition.

9. The composition as defined in claim 3 in the form of a lotion wherein said steroid is all-in-solution, said steroid being present in an amount within the range of from about 0.005 to about 0.6% by weight of the composition, said sebacate being present in an amount within the range of from about 5 to about 75% by weight of the composition.

10. The steroid composition as defined in claim 9 further including an emulsifier-thickener present in an amount within the range of from about 5 to about 14% by weight of the composition, a preservative present in an amount within the range of from about 0.05% to about 50% by weight of the composition, and water present in an amount within the range of from about 50 to about 90% by weight of the composition, and optionally including an anti-oxidant present in an amount within the range of from about 0.005 to about 0.1% by weight of the composition, and further optionally including an anti-whitening agent or anti-foaming agent present in an amount within the range of from about 0.2 to about 3% by weight of the composition.

11. The steroid composition as defined in claim 3 in the form of an ointment or gel wherein said steroid is present in an amount within the range of from about 0.001 to about 2% by weight of the composition, said sebacate vehicle is present in an amount within the range of from about 5 to about 75% by weight of the composition.

12. The steroid composition as defined in claim 11 further including an oleaginous material present in an amount within the range of from about 25 to about 95% by weight of the composition.

13. The steroid composition as defined in claim 12 further including one or more antioxidants.

14. A method of treating dermatitis, which comprises administering topically an effective amount of a composition as defined in claim 1.

15. A method of treating dermatitis, which comprises administering topically an effective amount of a composition as defined in claim 7.

16. A method of treating dermatitis, which comprises administering topically an effective amount of a composition as defined in claim 11.

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